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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,447	PINCHERA ET AL.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-15 and 17-25* is/are pending in the application.

4a) Of the above claim(s) *17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-15 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04-22-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114, received 09/29/08.

Status of the Claims

Claims 9-15 and 17-25 are currently pending in this application.

Claims 17-24 are withdrawn for examination purposes for being directed to non-elected subject matter.

Claims 9-15 and 25 are under examination.

Miscellaneous

It is noted that Form 326, mailed 04/29/08, incorrectly lists the withdrawn claims as "1-25" but correctly lists the rejected claims as "9-16 and 25." The inadvertent typographical error regarding the withdrawn claims is hereby corrected to show that "claims 17-24" are withdrawn from examination for being directed to non-elected subject matter.

The examiner would like to thank applicant for pointing out the above-referenced inadvertent typographical error (see applicant's Response, footnote 1).

Information Disclosure Statement

Upon re-consideration, applicant's information disclosure statement, received 04/22/05, has been considered and made of record.

Submission of Drawing

Applicant's Exhibit 1 (= Figure 5), received 09/29/08, showing the plasma concentrations of T3S and T3 after oral administration of T3S 21 μg/kg is acknowledged.

Response to applicant's arguments/response

Rejection under 103(a)

This rejection is withdrawn in view of applicant's persuasive arguments. It is noted that even though the grounds of the new rejections have been altered, the merit of the cited references are being maintained (see also applicant's Response, received 09/29/08, pages 2-6).

REJECTIONS

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopresti et al. (LoPresti. Characteristics of 3,5,3'-Triiodothyronine Sulfate Metabolism in Euthyroid Man. Journal of Clinical Endocrinology and Metabolism, Vol. 73, No. 4, 1992, pages 703-709; already made of record), in view of Miura et al. (US Patent 5,116,828; already made of record).

LoPresti et al. teach an oral composition comprising 25 µCi 3,5,3'-Triiodothyronine Sulfate (T3S) in 20 ml 1% albumin solution in distilled water (page 704, col. 2, third full para.). LoPresti et al. teach that in one of the two patients who ingested said composition, the amount of tracer collected in the urine was 5.4%, and 10.45 in 24 and 72 hours, respectively, following the ingestion of the composition (page 707, col. 1, first para.).

It is unclear if LoPresti et al. dosage falls within applicant's instantly claimed amount of T3S as recited in claims 9-10. It is requested that applicant provide the

conversion of µCi to µg, if applicant knows the conversion of µCi to µg since LoPresti dosage amount may in fact read on applicant's range..

Miura et al teach L-thyroxine in doses of 25-400 µg/day, and L-triiodothyronine (T3) in doses of 5-150 µg/day (see col. 3, lines 1-4).

It would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the Lopresti et al. and Miura et al. to manipulate the dosage amount of 3,5,3'-triiodothyronine sulfate (T3S) in the composition taught by LoPresti et al., including applicant's dosage range amount of 5 to 1000 µg, in preparing an oral composition comprising T3S to treat hypothyroidism. One would have been motivated to do so because Miura et al. suggest that the dosage range of thyromimetic drugs is very wide and T3S as taught by LoPresti et al. is also a thyromimetic drug. Besides, it is routine in the pharmaceutical art to formulate compositions comprising different amounts of active compounds depending on the intended purpose for administering the composition as well as for patient parameters. Further, one would be motivated to do so depending the specific patient factors such as the severity of the condition being treated, the patient's weight, and the patient's age, in order to minimize side effects and at the same time maximize the beneficial effects of the composition in view of the wide therapeutic dosage range of T3 as evidenced by the teaching of Miura et al.

Thus, it would have been within the scope of knowledge and skill of an artisan skilled in the art to manipulate the dose of T3S as taught by LoPresti et al. to arrive at

the instant claimed dosage of T3S without resorting to undue experimentation as evidenced by the teaching of Miura et al.

It is noted that the teaching of an oral composition comprising 25 µCI T3S as taught by LoPresti et al. (page 704, col. 2, third full para.) reads on the term "[a] pharmaceutical composition for oral administration comprising triiodothyronine sulfate" as recited in claim 9.

It is also noted that the teaching of a composition comprising 20 ml of a 1% albumin solution in distilled water as taught by LoPresti et al. reads on the instant claimed term "together with pharmaceutically acceptable additives selected from the group consisting of excipients, diluents, dissolvents, solvents, carriers, …" as recited in claim 9 because albumin and distilled water can serve the function, for example, as excipients/solvents/carriers (page 704, col. 2, third full para.).

With respect to the preamble, it is noted that the instant claims are directed to **a product** and not a method of using a product. To the extent that the prior art teaches each instantly claimed element, the structure of the composition encompassed by the prior art is capable of performing the intended function.

Claims 9-15 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Santini et al. Thyromimetic effects of 3,5,-3'-triiodothyronine sulfate in hypothyroid rats. Endocrinology. 1993;133(1): 105-110; already made of record by applicant), in view of Miura et al. (US Patent 5,116,828; already made of record).

Santini et al. (Santini et al. Thyromimetic effects of 3,5,-3'-triiodothyronine sulfate in hypothyroid rats. Endocrinology. 1993;133(1): 105-110; already made of record by applicant) teach that treatment of hypothyroid thyroidectomized (Tx) rats with T3S and T3 in doses of 0.46 and 2.3 nmol/day for 10 days via intraperitoneal (i.p.) injection results in marked improvement in the growth of the treated rats (abstract). Santini et al. concluded that administration of T3S to hypothyroid rats produces thyromimetic effects with a potency one fifth that of T3 (abstract). Santini et al. also teach that sulfatases have been found in tissues and the intestinal flora that convert T3S back to the parent hormone (T3S) and therefore T3S might represent a reserve pool of T3 to attenuate the effects of reduced generation of T3 from T4 under conditions where monodeiodinase (MD) activity is reduced e.g. fetal life, fasting, nonthyroidal illnesses, hypothryroidism, and selenium deficiency even though the exact amount of T3S that could be generated by desulfation of T3S is not known (page 105, col. 1, second para., lines 5-12). Santini et al. et al. further suggest that T3S may reduce the risk of inducing hyperthyroidism when compared to T4 and that more studies are necessary to test this possibility (page 109, first para., last three lines to last para., last line).

It is unclear if Santini et al dosage falls within applicant's instanly claimed amount of T3S as recited in claims 9-10. It is requested that applicant provide the conversion of nMol to µg of TS3

Although Santini et al. teach formulations comprising T3S, this reference does not teach compositions comprising T3S in the specific instantly claimed amount of 5 to

1000 µg. Further, Satini et al. do not teach the instant claimed combination of T3S and thyroxine.

The above discussions of Miura is incorporated by reference.

It would have been obvious to a person of skill in the art at the time the invention was made to manipulate the dosage amount of T3S in the composition taught by Santini et al., including applicant's claimed dosage amount of 5 to 1000 µg., based on patient parameters such as age, weight, and severity of condition. Besides, Santini et al. teach that T3S produces thyromimetic effects one fifth that of T3 (abstract). To the extent that Miura et al. teach L-triiodotyronine (T3) in doses of 5-150 µg/day, one would reasonably expect to administer T3S in an equivalent dosage amount of five times the T3 dose taught by Miura et al.(or 25 – 750 µg T3S) to treat hypothyroidism, which overlaps with the instant claimed dosage range of T3S (claims 9-10).

Further, it would have been obvious to a person of skill in the art at the time the invention was made to add thyroxine (T4) in a dosage range of 25-400 µg as taught by Miura et al. to the T3S composition as taught by Santini et al. for additive effects in treating hypothyroidism. One would have been motivated to do so because T3S as taught by Santini et al. and T4 as taught by Miura et al. are thyromimetic agents (see In re Kerkhoven, 205 USPQ 1069 (CCPPA 1980).

It is noted that the dosage range of 25-400 µg thyroxine taught by Miura et al. overlaps with the instant claimed thyroxine dosage range recited in claims 11, 13, 15, and 25.

With respect to claims 14, 15 and 25 which are directed to a kit, it is the examiner's position that it would have been obvious to a person of skill in the art at the time the invention was made to supply T3S and thyroxine the same package (= kit) for patient convenience. One would have been motivated to do so because by packaging T3S and thyroxine in the same package (= kit) would improve patient compliance because this would reduce the chances of a patient forgetting to take both agents.

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Response to applicant's arguments/remarks

In response to applicant's arguments that none of the prior art references teach or suggest the instant claimed oral T3S composition since the sulphate metabolite of T3 was known to be **biologically inactive**, it is the examiner's position that the instant claims are directed to a pharmaceutical composition, i.e. a product, and not a method of using a product. LoPresti et al. teach an oral composition comprising the identical instantly claimed compound, wherein said composition also comprises 1% albumin (e.g. carrier) and distilled water (= diluent/solvent). Thus, the combination of references teach all the claimed limitations, i.e. a composition comprising T3S that is orally administered. "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley. Further, the instant invention is not patentably distinct, i.e. structurally distinct from the prior art and thus, the rejection under 103(a) is proper.

With respect to applicant's argument that LoPresti et al. teach away from oral administration of T3S such that one would not have expected that T3S would exert thyromimetic activity, it is the examiner's position that even though LoPresti et al. teach that T3S itself is not biologically active, it would have been obvious to a person of skill in the art at the time the invention was made to combine T3S as taught by LoPresti et al. and thyroxine (=T4) as taught by Miura et al. to treat a patient with hypothyroidism in order to attenuate the effects of reduced generation of T3 from T4. One would have been motivated to do so because Santini et al. suggest that T3S may serve as a reserve pool to attenuate the effects of reduced generation of T3 from T4 in hypothyroidism and both T3 and T4 are thyromimetic agents. Besides, Santini et al. et al. further suggest that use of T3S as a source of T3 may reduce the risk on inducing hyperthyroidism when compared to T4 and that more studies are necessary to test this possibility (page 109, first para., last three lines to last para., last line).

Thus, applicant's Exhibit 1 (= Figure 5) showing plasma concentrations of T3S and T3 after oral administration of T3S 21 μg/kg are considered to be expected results because one would reasonably expect that it would take longer for the sulfatases in the intestinal flora to convert a high orally administered dose of T3S as exemplified by applicant in Exhibit I as compared to the low dose of T3S as taught by Lopresti et al. and that increasing the dose of a drug would reasonably result in higher drug levels. Hence, the detectable levels of T3S disclosed by applicant is simply a reflection of the delayed conversion of the T3S to T3 due to administration of the higher dose of T3S. However, it is routine in the medical art to manipulate the dose of drugs by conducting

pharmacokinetic studies to determine the bioavailability of pharmaceutical compositions and therefore it would have been with the scope of knowledge and skill of an artisan skilled in the art at the time the invention was made to conduct bioavailability studies of formulations comprising T3S by manipulating the dose of T3S, including applicant's claimed dosage range, to optimize the bioavailability of orally administered T3S because Santini et al. suggest that T3S is a source of T3 and that T3S may be associated with a reduced risk of inducing hyperthyroidism when compared with T4.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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9 December 2008

/C. R./ Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611